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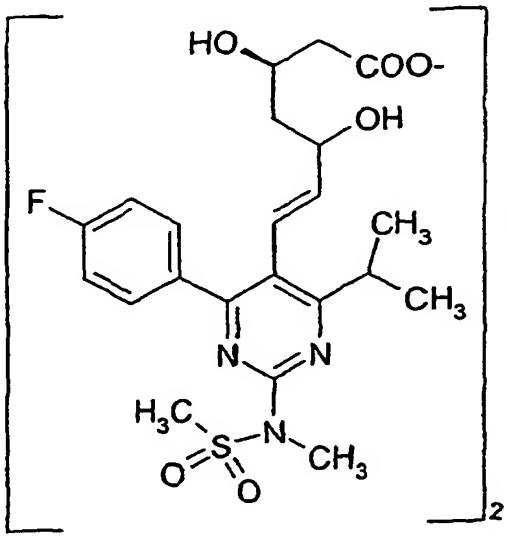
(54) Title: AMORPHOUS SALTS OF ROSUVASTATIN



(I)

(57) Abstract: The invention provides the novel amorphous rosuvastatin magnesium and process for preparation thereof from crystalline rosuvastatin magnesium, rosuvastatin methyl ammonium salt and from rosuvastatin lactone. Rosuvastatin magnesium is, chemically, (3R,5S,6E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, magnesium salt (2:1) of Formula (I). Rosuvastatin magnesium is an antihypercholesterolemic drug used in the treatment of atherosclerosis.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

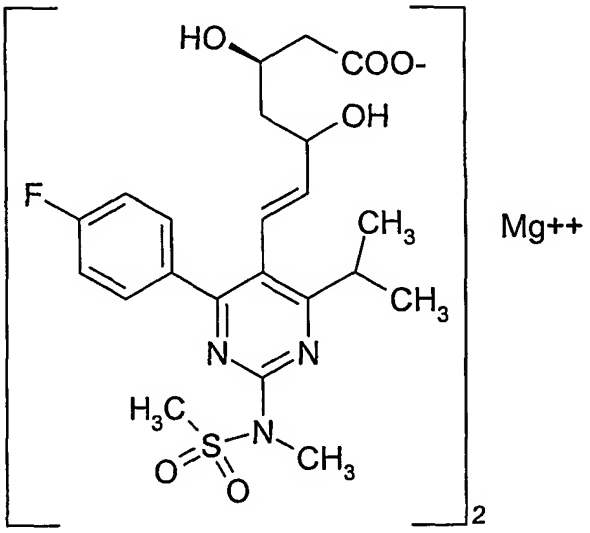
AMORPHOUS MAGNESIUM SALTS OF ROSUVASTATIN

Field of the Invention

This invention relates to amorphous salts of HMG CoA reductase inhibitors, and in particular, amorphous rosuvastatin magnesium, and processes for preparation thereof from crystalline rosuvastatin magnesium, rosuvastatin methyl ammonium salt and from rosuvastatin lactone.

Background of the Invention

Rosuvastatin magnesium is, chemically, (3R,5S,6E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, magnesium salt (2:1) of Formula I.



FORMULA I

Rosuvastatin magnesium is an antihypercholesterolemic drug used in the treatment of atherosclerosis.

The difference in the activity of different polymorphic forms of a given drug has drawn the attention of many workers in recent years to undertake the studies on polymorphism. This has especially become very interesting since many antibiotics, antibacterials, tranquilizers exhibit polymorphism and particular polymorphic forms of a given drug can exhibit superior bioavailability and consequently show much higher

activity compared to other forms. The term polymorphism includes different physical forms, crystal forms, and crystalline / liquid crystalline / non-crystalline (amorphous) forms.

It has also been disclosed that the amorphous forms in a number of drugs can exhibit different dissolution characteristics and in some cases, different bioavailability patterns compared to the crystalline form [Konne T., *Chem. Pharm. Bull.*, 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. Cefuroxime axetil is a classical example of an amorphous form exhibiting higher bioavailability than a crystalline form.

US Patent No. RE37314 describes a process for preparation of amorphous rosuvastatin calcium by dissolving the corresponding sodium salt in water, adding calcium chloride, and collecting the resultant precipitate by filtration.

US Patent No. 6,589,959 describes a process for preparation of crystalline form A of rosuvastatin by warming the amorphous form of rosuvastatin calcium in a mixture of water and acetonitrile, cooling the resultant solution to ambient temperature and then filtering the product which is then dried at 50°C under vacuum to give crystalline Form A of rosuvastatin calcium.

The preparation of crystalline rosuvastatin magnesium salt is described in PCT patent application WO 01/60804 from rosuvastatin methyl ammonium salt of Formula II.

Rosuvastatin methyl ammonium salt is treated with sodium hydroxide in water to get free rosuvastatin acid, which is then reacted, with magnesium sulphate to get rosuvastatin magnesium salt, which is then isolated and dried. The dried magnesium salt is then heated with water and after diluting the reaction mass with water; the resultant solution is then allowed to stand for 66 hours followed by filtration of the crystalline magnesium salt.

Amorphous rosuvastatin salts can be more effective pharmaceutically than the corresponding crystalline forms. Amorphous forms can be very difficult to isolate and can pose problems with respect to purity and impurity profile. Amorphous forms can also

have stability issued and can convert to more stable crystalline forms by absorption of moisture from atmosphere.

Summary of the Invention

The present inventors have set out to prepare heretofore unknown amorphous rosuvastatin magnesium having a high purity. In one aspect, stable amorphous rosuvastatin magnesium is provided.

It has been discovered that amorphous rosuvastatin magnesium when made by the processes of the present invention is easy to isolate and handle, thus making the process amenable for commercial scale use. The purity of the amorphous rosuvastatin magnesium of the present invention is greater than 99%, with diastereomeric impurity less than 0.5%.

Brief Description of the Drawings

Figure 1 is an X-ray powder diffraction (XRD) pattern of amorphous rosuvastatin magnesium.

Figure 2 is an X-ray powder diffraction (XRD) pattern of crystalline rosuvastatin magnesium.

Figure 3 is an X-ray powder diffraction (XRD)` pattern of a mixture of largely amorphous mixed with some crystalline rosuvastatin magnesium.

Figure 4 is an X-ray powder diffraction (XRD) pattern of amorphous rosuvastatin calcium.

Figure 5 is an X-ray powder diffraction (XRD) pattern of crystalline rosuvastatin calcium.

In one aspect, amorphous rosuvastatin magnesium of Formula I is provided.

The purity of the amorphous form is greater than 99%, with diastereomeric impurity less than 0.5%. For example, the purity is greater than 99.5%, with diastereomeric impurity less than 0.25%, or for example the purity is greater than 99.8%, with diastereomeric

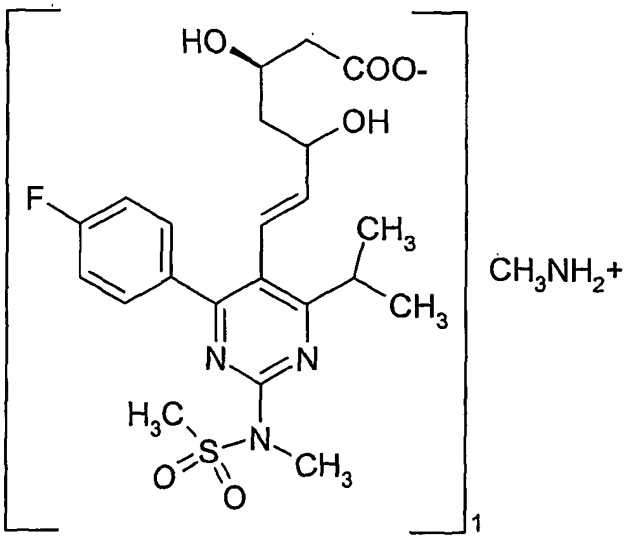
impurity less than 0.15%. Amorphous rosuvastatin magnesium substantially free of crystalline rosuvastatin magnesium is also provided herein.

In another aspect, an improved process for the preparation of crystalline rosuvastatin magnesium from rosuvastatin methyl ammonium salt or from rosuvastatin lactone is provided. The process comprises

a) treating rosuvastatin methyl ammonium salt or rosuvastatin lactone with a base and magnesium salt.

b) isolating crystalline rosuvastatin magnesium from the reaction mass.

Rosuvastatin methyl ammonium salt of Formula II

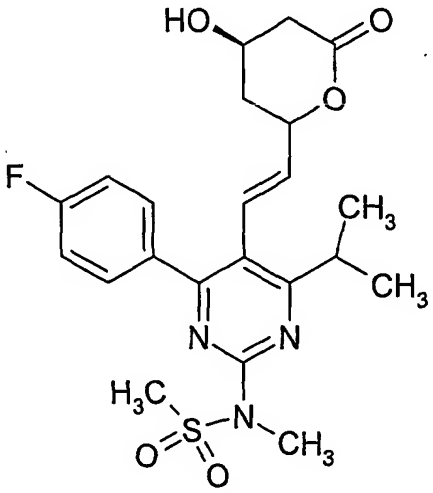


FORMULA II

can be prepared by the process described in PCT application WO 01/60804. Rosuvastatin methyl ammonium salt can be treated with a base in presence of water optionally containing an organic solvent. The reaction mass can then be partially concentrated to remove excess methylamine or ammonia liberated. The reaction mass can then be treated with a compound capable of generating magnesium ions, at a temperature of about 20 to 45°C under stirring. The solution can then finally be cooled to room temperature and filtered to get crystalline rosuvastatin magnesium. The entire process can be carried out in-situ without isolating any other salt of rosuvastatin, such as sodium or calcium. As per the

process described in Example 9 of PCT application WO 01/60804, the product obtained can further be crystallized from water, which generally involves 4 hours of stirring, and about 66 hours of standing, followed by filtration. However, there is no need to further purify the crystalline rosuvastatin magnesium obtained by the process provided herein. Thus, the process of present invention is less time-consuming and simple to operate on a commercial scale.

Alternatively, rosuvastatin lactone of Formula III,



FORMULA III

is treated with a base in the presence of water optionally containing an organic solvent, at a temperature of about 20 to 45°C till hydrolysis of lactone is completed. The organic solvent can be then completely or partially removed. The resultant reaction mass can then be treated with a compound capable of generating magnesium ions at a temperature of about 20 to 45°C under stirring. The solution can then finally be cooled to room temperature and filtered to get crystalline rosuvastatin magnesium. The entire process can be carried out in-situ without isolating any other salt of rosuvastatin, such as sodium or calcium.

The crystalline rosuvastatin magnesium obtained can have a purity above about 99% with diastereomeric impurities less than about 0.5%, for example purity above 99.25% with diastereomeric impurities less than 0.25%. The crystalline material can be

used as such for the purpose of preparing medicament and also for the preparation of amorphous rosuvastatin magnesium or amorphous rosuvastatin calcium.

The base is selected from, for example, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate.

The magnesium ions can be generated by using a magnesium compound selected from, for example, magnesium chloride, magnesium hydroxide, magnesium carbonate, magnesium acetate, magnesium sulphate, magnesium borate, magnesium tartarate, magnesium bromide or any other compound capable of generating magnesium ions.

The organic solvent can comprise lower alkanols, ethers, esters, ketones, polar aprotic solvents, alkyl or cycloalkyl hydrocarbons or mixtures thereof. The lower alkanol can be, for example, methanol, ethanol, isopropanol, isobutanol, n-butanol and n-propanol. The ethers can be, for example, tetrahydrofuran, 1,4-dioxane, diethyl ether and diisopropyl ether. The esters can be, for example, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone. Alkyl or cycloalkyl hydrocarbons can be, for example, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane or mixtures thereof.

In another aspect, a process for preparation of crystalline rosuvastatin magnesium from rosuvastatin methyl ammonium salt of Formula II is provided.

The process comprises

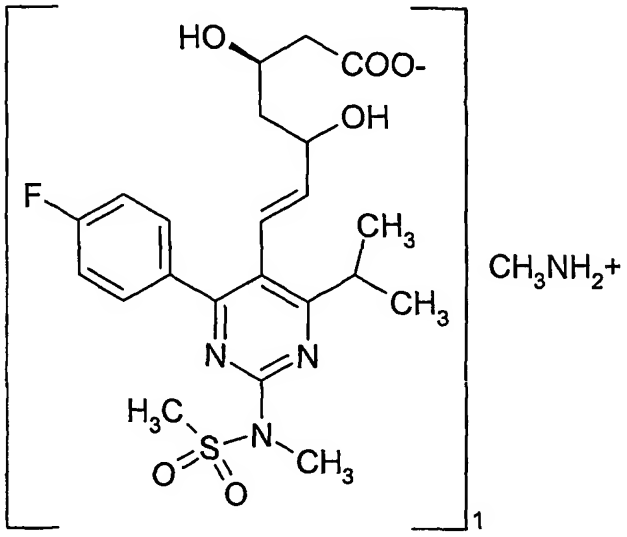
a) lactonizing the rosuvastatin methyl ammonium salt of Formula II to give rosuvastatin lactone of Formula III;

b) optionally isolating the rosuvastatin lactone of Formula III;

c) converting the rosuvastatin lactone to the rosuvastatin magnesium by treatment with a base and a magnesium salt; and

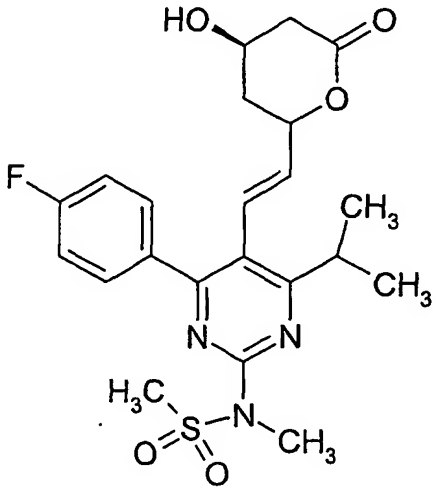
d) recovering the crystalline rosuvastatin magnesium from the reaction mass.

Rosuvastatin methyl ammonium salt of Formula II,



FORMULA II

can be prepared by the process described in PCT application WO 01/60804. Rosuvasatin methyl ammonium salt can be treated with an acid (pH of about 1 to 5) to get rosuvastatin lactone of Formula III



FORMULA III

The reaction can be carried out in presence of a first organic solvent, optionally containing water, at a temperature of about -10 to 100°C. After completion of the reaction, the layers are separated and organic layer after washing with water and/or brine can be concentrated

under vacuum. The residue can be taken up in a second organic solvent. The mixture can be stirred at a temperature of about 40 to about 150°C for about 1 to 50 hours to affect lactonization. After completion of lactonization, the second organic solvent can be removed from the reaction mass under vacuum and the residue can be treated with third organic solvent to get the rosuvastatin lactone. The residue can be taken directly to the next step without actually isolating the lactone.

The acid can be, for example, an inorganic mineral acid such as hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid, or an organic acid such as formic acid, acetic acid and the like.

The first organic solvent can be, for example, water immiscible or partially miscible organic solvent such as, for example, toluene, xylene, benzene, ethyl methyl ketone, diisobutyl ketone, methyl isobutyl ketone, methyl t-butyl ether, diisopropyl ether, ethyl acetate, methyl formate, methyl acetate, isobutyl acetate, n-propyl acetate, isopropyl acetate, amyl acetate or mixtures thereof.

The second organic solvent can be, for example, methyl t-butyl ether, toluene, xylene, benzene, diisopropyl ether, n-butanol, isobutyl acetate, ethyl methyl ketone, diisobutyl ketone or mixtures thereof.

The third organic solvent in which rosuvastatin is insoluble or very slightly soluble or sparingly soluble can be, for example, isopropanol, isobutanol, n-butanol, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof. Herein, wherever the term insoluble, very slightly soluble or sparingly soluble is mentioned, it is in accordance with the description provided in the United States Pharmacopoeia 2002.

The conversion of rosuvastatin lactone to crystalline rosuvastatin magnesium can be carried out as described above.

In another aspect, a process for preparing amorphous rosuvastatin magnesium from crystalline formis provided. The process comprises

a) dissolving the crystalline form in a suitable organic solvent;

b) removing solvent from the said solution; and

c) recovering amorphous rosuvastatin magnesium.

Crystalline rosuvastatin magnesium can be prepared by methods described above. The crystalline form can be dissolved in an organic solvent. The solvent can then be removed from the solution to get amorphous rosuvastatin magnesium. The amorphous rosuvastatin magnesium thus obtained can be dried using conventional drying techniques such as vacuum tray drying, rotary vacuum drying, fluidized bed drier, tray drying and the like.

The organic solvent can be, for example, lower alkanols, ethers, esters, ketones, polar aprotic solvents or mixtures thereof. The lower alkanol can be, for example, methanol, ethanol, isopropanol and n-propanol. The ethers can be, for example, tetrahydrofuran and 1,4-dioxane. The esters can be, for example, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

The solution of crystalline rosuvastatin magnesium can be prepared in the organic solvent by optional warming to dissolve the solids. If required, the solution can be clarified to remove the undissolved foreign particulate matter. The solution can then be concentrated to remove solvent. The concentration can be carried out under vacuum of about 100 to about 0.01 mm of Hg wherein the solvent is removed by vacuum distillation while optionally heating the solution at a temperature of about 15 to about 55°C to effect faster removal of the solvent.

The solvent can also be removed by spray-drying the solution of crystalline rosuvastatin calcium using a spray-dryer. For the purpose of spray-drying, mini-spray Dryer (Model: Buchi 190 Switzerland) which operates on the principle of nozzle spraying in a parallel - flow i.e. the sprayed product and the drying gas flow in the same direction

can be used, for example. The drying gas can be air or inert gases such as nitrogen, argon or carbon dioxide.

In another aspect, a process for preparing amorphous rosuvastatin magnesium from crystalline form is provided. The process comprises

a) dissolving the crystalline form of rosuvastatin magnesium in a suitable first organic solvent;

b) adding a second organic solvent to the solution of rosuvastatin magnesium or adding the solution of rosuvastatin magnesium to the second organic solvent (in optional order of succession) in which rosuvastatin magnesium is insoluble or very slightly soluble or sparingly soluble, such that amorphous rosuvastatin magnesium precipitates out from the solution; and

c) isolating the amorphous rosuvastatin magnesium from the mixture.

Crystalline rosuvastatin magnesium can be dissolved in a first organic solvent and to the solution added a second solvent or added solution of rosuvastatin magnesium to the second organic solvent (in optional order of succession) in which rosuvastatin is insoluble or very slightly soluble or sparingly soluble. Due to addition of the second solvent, rosuvastatin magnesium precipitates out from the solution. The precipitated product can then be isolated and dried by conventional techniques to get the amorphous rosuvastatin magnesium.

The suitable first organic solvent can be for example lower alkanols, ethers, esters, ketones, polar aprotic solvents or mixtures thereof. The lower alkanol can be, for example, methanol, ethanol, isopropanol and n-propanol. The ethers can be, for example, tetrahydrofuran and 1,4-dioxane. The esters can be, for example, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

The second organic solvent in which rosuvastatin is insoluble (10,000 and over parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) or very slightly soluble (form 1,000 to 10,000 parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) or sparingly soluble (from 30 to 100 parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) can be, for example, isopropanol, isobutanol, n-butanol, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof.

In another aspect, a process for preparation of amorphous rosuvastatin magnesium from crystalline rosuvastatin magnesiumis provided. The process comprises

a) dissolving the crystalline rosuvastatin magnesium in a suitable organic solvent;

b) adding water to the solution of rosuvastatin magnesium, or adding the solution of rosuvastatin magnesium to water (in optional order of succession), such that rosuvastatin magnesium precipitates out from the solution; and

c) isolating the amorphous rosuvastatin magnesium from the mixture.

Crystalline rosuvastatin magnesium can be dissolved in an organic solvent and the solution can be optionally treated with charcoal or clarified to remove foreign particulate matter. The clear solution can be obtained by gently warming the mixture as well. To the clear solution water can be added at such a rate that rosuvastatin magnesium precipitates slowly. The mixture after complete addition of water can be chilled or partially concentrated to remove the organic solvent. The separated amorphous form can then be filtered and dried as per the methods described earlier.

The suitable organic solvent can be, for example, methanol, ethanol, isopropanol, n-propanol, tetrahydrofuran, 1,4-dioxane, acetone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone or mixtures thereof.

In another aspect, a process for preparing amorphous rosuvastatin magnesium from crystalline form is provided. The process comprises:,

a) subjecting crystalline rosuvastatin magnesium to milling until the crystalline form is converted to amorphous form; and

b) optionally drying the amorphous form.

Crystalline rosuvastatin magnesium solid or its slurry in an organic solvent can be milled by grinding between two surfaces. Such milling can be carried out by using a traditional technique of compounding using a pestle and mortar or by milling machines that essentially use the same principle. Examples of such milling machines include various makes of ball mills, roller mills, gyratory mills, and the like. The slurry of crystalline rosuvastatin magnesium in an organic solvent can be of 30 to 85% w/v.

The organic solvent in which rosuvastatin is insoluble or very slightly soluble or sparingly soluble can be, for example, isopropanol, isobutanol, n-butanol, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof.

In another aspect, a process for preparing amorphous rosuvastatin magnesium from crystalline form is provided. The process comprises:

a) dissolving crystalline rosuvastatin magnesium in an organic solvent optionally containing water; and

b) freeze drying or lyophilizing the solution to get amorphous rosuvastatin magnesium.

A solution of crystalline rosuvastatin magnesium in an organic solvent optionally containing water can be prepared and treated with charcoal, filtered to remove charcoal. The clear solution is then freeze-dried by conventional techniques to get the amorphous rosuvastatin magnesium. The amorphous form can then be dried under vacuum.

The organic solvent can be, for example, lower alkanols, ethers, esters, ketones, polar aprotic solvents or mixtures thereof. The lower alkanol can be, for example,

methanol, ethanol, isopropanol and n-propanol. The ethers are selected from tetrahydrofuran and 1,4-dioxane. The esters can be, for example, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

In another aspect, a process for preparation of amorphous rosuvastatin magnesium from rosuvastatin methyl ammonium salt of Formula II is provided. The process comprises:

a) lactonizing the rosuvastatin methyl ammonium salt of Formula II;

b) optionally isolating the rosuvastatin lactone of Formula III;

c) converting the lactone form of rosuvastatin to rosuvastatin magnesium by treatment with a base and a magnesium salt;

d) removing the water from the reaction mass by azeotropic distillation using an organic solvent; and

e) recovering the amorphous form of rosuvastatin magnesium by removing the organic solvent from the resultant solution.

Rosuvastatin methyl ammonium salt can be converted to rosuvastatin magnesium as described above. However, after treating the aqueous layer with magnesium ions, to the reaction mass is added a suitable organic solvent capable or azeotropically removing water and simultaneously capable of dissolving rosuvastatin magnesium. From the resulting mixture, water was removed and from the solution of rosuvastatin magnesium, solvent was removed to get the desired amorphous rosuvastatin magnesium as solid.

Alternatively after treatment with magnesium ions, to the reaction mass is added an organic solvent which dissolves rosuvastatin magnesium and is immiscible or partially

miscible with water. The solvent can be made immiscible in water by increasing the salinity of the aqueous layer, using for example,sodium chloride or calcium chloride. The layers can be separated and the organic layer containing rosuvastatin magnesium can then be dried, for example, over magnesium sulphate, sodium sulphate or molecular sieves to remove traces of water. The organic layer can then be concentrated to remove solvent, and get the desired amorphous rosuvastatin magnesium. The concentration can be effected by either spray drying or by vacuum distillation.

The organic solvent can be, for example, tetrahydrofuran, 1,4-dioxane, toluene, xylene, dichloromethane, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate, amyl acetate, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone or mixtures thereof.

In another aspect, a process of preparation of amorphous rosuvastatin magnesium from crystalline form is provided. The process comprises:

a) treating crystalline rosuvastatin magnesium with an acid to obtain rosuvastatin;

b) optionally isolating rosuvastatin;

c) converting rosuvastatin to rosuvastatin magnesium by treatment with a base and magnesium salt;

d) removing water from the reaction mass by azeotropic distillation using an organic solvent; and

e) recovering the amorphous form of rosuvastatin magnesium by removing the organic solvent from the resultant solution.

Crystalline rosuvastatin magnesium can be treated with an acid to get rosuvastatin acid. The conversion can be easily carried out in presence of water optionally containing an organic solvent. The reaction temperature can be kept at about -5 to 100°C for example.

The organic solvent can be, for example, lower alkanols, ethers, esters, ketones, polar aprotic solvents, alkyl or cycloalkyl hydrocarbons or mixtures thereof. The lower

alkanol can be, for example, methanol, ethanol, isopropanol, isobutanol, n-butanol and n-propanol. The ethers can be, for example, tetrahydrofuran, 1,4-dioxane, diethyl ether and diisopropyl ether. The esters can be, for example, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone. Alkyl or cycloalkyl hydrocarbons can be, for example, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane or mixtures thereof.

After completion of the reaction the aqueous layer can be extracted with organic solvent, as described above. The organic layer after evaporation of solvent under vacuum gives rosuvastatin acid as oily residue. The residue can be dissolved in water and organic solvent and treated with a base and magnesium ions to get rosuvastatin magnesium. To the reaction mass can be added a suitable second organic solvent capable of azeotropically removing water and simultaneously capable of dissolving rosuvastatin magnesium. From the resulting mixture water was removed and from the solution of rosuvastatin magnesium, solvent was removed to get the desired amorphous rosuvastatin magnesium as solid.

Alternatively after treatment with magnesium ions, to the reaction mass can be added a second organic solvent which dissolves rosuvastatin magnesium and is immiscible or partially miscible with water. The solvent can be made immiscible in water by increasing the salinity of the aqueous layer using, for example, sodium chloride or calcium chloride. The layers are separated and the organic layer containing rosuvastatin magnesium is then dried over magnesium sulphate, sodium sulphate or molecular sieves to remove traces of water. The organic layer can then be concentrated to remove solvent to get the desired amorphous rosuvastatin magnesium. The concentration can be effected by either spray-drying or by vacuum distillation.

The second organic solvent can be, for example, tetrahydrofuran, 1,4-dioxane, toluene, xylene, dichloromethane, ethyl formate, methyl acetate, ethyl acetate, isopropyl

acetate, n-propyl acetate, isobutyl acetate, butyl acetate, amyl acetate, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone or mixtures thereof.

The examples of base and magnesium salt are described in above.

The acid used can be, for example, inorganic acid such as hydrochloric acid, sulphuric acid, phosphoric acid, hydrobromic acid, nitric acid and the like or a mixture thereof; or an organic acid, such as formic acid, acetic acid, propionic acid, anhydrides of carboxylic acids, methanesulphonic acid, 4-toluenesulphonic acid and the like.

In another aspect, a process for preparation of amorphous rosuvastatin magnesium from rosuvastatin methyl ammonium salt of Formula II is provided. The process comprises:,

a) treating the methyl ammonium salt form of rosuvastatin with a base and a calcium salt;

b) removing the water from the reaction mass by azeotropic distillation using an organic solvent; and

c) recovering the amorphous form of rosuvastatin calcium by removing the organic solvent from the resultant solution.

Rosuvastatin methyl ammonium salt can be converted to rosuvastatin magnesium as described above. However, after treating the aqueous layer with magnesium ions, to the reaction mass can be added a suitable organic solvent capable of azeotropically removing water and simultaneously capable of dissolving rosuvastatin magnesium. From the resulting mixture water can be removed and from the solution of rosuvastatin calcium, solvent can be removed to get the desired amorphous rosuvastatin magnesium as solid.

Alternatively after treatment with magnesium ions, to the reaction mass can be added an organic solvent which dissolves rosuvastatin magnesium and is immiscible or partially miscible with water. The solvent can be made immiscible in water by increasing the salinity of the aqueous layer using, for example, sodium chloride or calcium chloride.

The layers are separated and the organic layer containing rosuvastatin calcium is then dried over calcium chloride, sodium sulphate or molecular sieves to remove traces of water. The organic layer can then be concentrated to remove solvent to get the desired amorphous rosuvastatin magnesium. The concentration can be effected by either spray-drying or by vacuum distillation.

The organic solvent can be, for example, tetrahydrofuran, 1,4-dioxane, toluene, xylene, dichloromethane, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate, amyl acetate, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone or mixtures thereof.

In another aspect, a process for converting a mixture of amorphous and crystalline form of rosuvastatin magnesium to completely amorphous rosuvastatin magnesium is provided.

A mixture of largely amorphous with some crystalline rosuvastatin magnesium can be prepared directly from the rosuvastatin lactone or rosuvastatin methyl ammonium salt or from the crystalline form by the process already described in the specification with little variations. The crystalline rosuvastatin magnesium can be converted to a mixture of amorphous and crystalline material by techniques described above.

The mixture of largely amorphous rosuvastatin magnesium containing some crystalline form can then be converted to the amorphous form by techniques described Above.

In another aspect, the use of amorphous rosuvastatin magnesium in the preparation of rosuvastatin calcium either in crystalline or in amorphous form is provided. The aspect further provides a process for preparation of rosuvastatin calcium from amorphous rosuvastatin magnesium. The process comprises

a) reating amorphous rosuvastatin magnesium with a base and a calcium salt; and

b) isolating rosuvastatin calcium from the reaction mass.

The amorphous rosuvastatin magnesium can be treated with a base in presence of water optionally containing an organic solvent. The resultant mass can be concentrated partially to remove the organic solvent, followed by addition of the solution of calcium salt in water under vigorous stirring at such a rate that amorphous rosuvastatin calcium separates out from the reaction mass slowly. After complete addition the mass can be further stirred at temperature of about 10 to 30°C for about 1 to about 10 hours and filtered to get amorphous rosuvastatin calcium, which can be dried, for example, under vacuum.

The amorphous rosuvastatin calcium can then be crystallized by methods described in, for example, US Patent No. 6,589,959 to get crystalline rosuvastatin calcium which can be further converted to amorphous rosuvastatin calcium by methods described in, for example, co-pending Indian application 1304/DEL/2003.

In another aspect, amorphous rosuvastatin magnesium having an X-ray diffraction pattern as depicted in Figure I is provided.

In another aspect, pharmaceutical compositions and dosage forms comprising the amorphous rosuvastatin magnesium to be used as HMG-CoA reductase inhibitor in treatment of hyperlipidemia are provided.

In another aspect, a method inhibiting HMG-CoA enzyme in treatment of hyperlipidemia, comprising administering to a mammal in need thereof a therapeutically effective amount of the amorphous rosuvastatin magnesium is provided.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of Crystalline Rosuvastatin Magnesium from Rosuvastatin Methyl Ammonium Salt

Rosuvastatin methyl ammonium salt of Formula II (10 g) was added into water (50 ml) and to the resultant mass added a solution of aqueous sodium hydroxide (9 ml, 8% w/v) at 25-30oC and stirred for further 30 min. The solution was filtered through celite bed and the bed was washed with water (20 ml). The reaction mass concentrated to

recover water (40 ml) under vacuum at 60°C. To the reaction mass was added water (40 ml) and the equivalent quantity of water was removed under vacuum. The final solution was diluted with water (50 ml). To the solution after dilution with water was added aqueous solution of magnesium diacetate tetrahydrate (2.5 g, 20%) at 35°C with vigorous agitation. The resultant mass was further stirred for 1 hour at room temperature and solid crystalline product was collected by filtration. The product was dried under vacuum at 50°C.

Yield: 7.8 g (80%) (XRD as per Figure 2 showed it to be crystalline material)

HPLC Purity: 99.51%

Diastereomeric impurity: 0.27%

Example 2: Preparation of Crystalline Rosuvastatin Magnesium from Rosuvastatin Lactone

Rosuvastatin lactone of Formula III (5.0 g) was suspended in methanol (50 ml) and water (25 ml) at 25-30°C. To this mixture was added solution of aqueous sodium hydroxide (4.5 ml, 8% w/v) at 25-30°C and then further stirred at 35°C for 1 hour. After complete hydrolysis of lactone, methanol was recovered under reduced pressure at temperature below 45°C. To this solution was added water (15 ml) and a solution of magnesium diacetate tetrahydrate (1.34 g) in water (5 ml) at 35°C under vigorous agitation. The reaction mass was further stirred for 1 hour at 35°C and then cooled to 25-30°C. After complete precipitation of magnesium salt, it was filtered and the cake was washed with water (15 ml). The product was dried at 45 to 50°C.

Yield: 4.8 g (85%) (XRD as per Figure 2 showed it to be crystalline material)

Example 3: Preparation Of Crystalline Rosuvastatin Magnesium From Rosuvastatin Methyl Ammonium Salt

Step A) Preparation of Rosuvastatin Lactone from Rosuvastatin Methyl Ammonium Salt.

Rosuvastatin methyl ammonium salt (20 gm) was added into mixture of ethyl acetate (100 ml) and water (200 ml) at 25-30°C and the pH of the reaction mass was adjusted to about 3.0 with 6N hydrochloric acid. The layers were separated and the organic layer is washed with water (50 ml). The organic layer was concentrated under vacuum to get an oily crude product, which was mixed with toluene (50 ml). The reaction mass was refluxed for about 6 hours and the solvent was removed under vacuum at 60°C. The residue obtained was stirred with hexane (100 ml) and the separated solid was filtered. Dried the product under vacuum till constant weight at 40-45°C to get rosuvastatin lactone.

Step B) Preparation of Crystalline Rosuvastatin Magnesium from Rosuvastatin Lactone

Rosuvastatin lactone of Formula III (5.0 g) was suspended in methanol (50 ml) and water (25 ml) at 25-30°C. To this mixture was added solution of aqueous sodium hydroxide (4.5 ml, 8% w/v) at 25-30°C and then further stirred at 35°C for 1 hour. After complete hydrolysis of lactone, methanol was recovered under reduced pressure at temperature below 45°C. To this solution was added water (15 ml) and a solution of magnesium diacetate tetrahydrate (1.34 g) in water (5 ml) at 35°C under vigorous agitation. The reaction mass was further stirred for 1 hour at 35°C and then cooled to 25-30°C. After complete precipitation of magnesium salt, it was filtered and the cake was washed with water (15 ml). The product was dried at 45 to 50°C.

Yield: 4.8 g (85%) (XRD as per Figure 2 showed it to be crystalline material)

Example 4: Preparation of Amorphous Rosuvastatin Magnesium from Crystalline Rosuvastatin Magnesium By Vacuum Drying

Crystalline Rosuvastatin magnesium (2.0 g) was dissolved in tetrahydrofuran (5 ml) at 25-30°C. The solution was filtered through celite bed to get a clear solution of rosuvastatin magnesium in tetrahydrofuran and the celite bed was washed with tetrahydrofuran (2 ml). The clear solution was then concentrated and solvent was recovered under vacuum at 45°C to get the title product.

Yield: 1.9 g (95%) (XRD as per Figure 1 showed it to be amorphous material)

HPLC Purity: 99.41%

Diastereomeric impurity: 0.34%

Example 5: Preparation of Amorphous Rosuvastatin Magnesium from Crystalline Rosuvastatin Magnesium By Spray Drying

Crystalline Rosuvastatin magnesium (5.0 g) was dissolved in tetrahydrofuran (25 ml) at 25-30°C. The solution was filtered through celite bed to get a clear solution of rosuvastatin magnesium in tetrahydrofuran and the celite bed was washed with tetrahydrofuran (2 ml). The clear solution obtained was fed in to spray drier at 25-30°C at nitrogen flow rate of 600 Newtonlitre per hr and product was collected and dried under vacuum at 45°C.

Yield: 4.5 g (90%) (XRD as per Figure 1 showed it to be amorphous material)

Example 6: Preparation of Amorphous Rosuvastatin Magnesium from Crystalline Rosuvastatin Magnesium By Precipitation

Crystalline Rosuvastatin magnesium (2.0 g) was dissolved in tetrahydrofuran (5 ml) at 25-30°C. The solution was filtered through celite bed to get a clear solution of rosuvastatin magnesium in tetrahydrofuran and the celite bed was washed with tetrahydrofuran (2 ml). The resultant solution was poured dropwise into cyclohexane (60 ml) under vigorous agitation after which the mixture was further stirred for 30 min.

The solid product which precipitated was filtered at 25-30°C under nitrogen and dried under vacuum at 45°C.

Yield: 1.7 g (85%) (XRD as per Figure 1 showed it to be amorphous material)

HPLC Purity: 99.27% Diastereomeric impurity: 0.41%

Example 7: Preparation of Amorphous Rosuvastatin Magnesium from Crystalline Rosuvastatin Magnesium By Milling

Crystalline rosuvastatin magnesium (2.0 gm) was slurried in cyclohexane (10 ml) and the slurry was placed in a glass mortar. The slurry was triturated with pestle till the crystalline form was completely converted to amorphous form. The slurry was then filtered and the solid was dried under vacuum at 40-45°C to get amorphous rosuvastatin magnesium.

Yield: 1.3 gm (65%) (XRD as per Figure 1 showed it to be an amorphous material)

Example 8: Preparation of Rosuvastatin Magnesium Amorphous grom Crystalline Rosuvastatin Magnesium By Freeze Drying

Crystalline rosuvastatin magnesium (1.0 g) was dissolved in 1,4 dioxane (5 ml) by gently warming at 38°C. The solution was placed in a bath containing acetone and dry ice maintained at about -20 to -30°C and cooled to –20°C under rotation. The material was solidified by cooling and then vacuum of less than 0.1 mm of Hg was applied. The temperature of the bath was slowly raised from –20 to 10°C over 2 hours while under vacuum. Further temperature was raised to 10 to 25°C over 1 hour. Title compound was obtained was dried under vacuum at 45°C.

Yield: 0.85 g (85%) (XRD as per Figure 1 showed it to be amorphous material)

Example 9: Preparation of Amorphous Rosuvastatin Magnesium from Rosuvastatin Methyl Ammonium Salt

Step A) Preparation of Rosuvastatin Lactone from Rosuvastatin Methyl Ammonium Salt.

Rosuvastatin methyl ammonium salt (20 gm) was added into a mixture of ethyl acetate (100 ml) and water (200 ml) at 25-30°C and the pH of the reaction mass was adjusted to about 3.0 with 6N hydrochloric acid. The layers were separated and the organic layer washed with water (50 ml). The organic layer was concentrated under vacuum to get an crude oily product, which was mixed with toluene (50 ml). The reaction mass was refluxed for about 6 hours and the solvent was removed under vacuum at 60°C. The residue obtained was stirred with hexane (100 ml) and the separated solid was filtered. Dried the product under vacuum to constant weight at 40-45°C to get rosuvastatin lactone.

Step B) Preparation of Amorphous Rosuvastatin Magnesium from Rosuvastatin Lactone

Rosuvastatin lactone of Formula III (5.0 g) was suspended in methanol (50 ml) and water (25 ml) at 25-30°C. To this mixture was added solution of aqueous sodium hydroxide (4.5 ml, 8% w/v) at 25-30°C and then further stirred at 35°C for 1 hour. After complete hydrolysis of lactone, methanol was recovered under reduced pressure at temperature below 45°C. To this solution was added water (15 ml) and aqueous solution of Magnesium diacetate tetrahydrate (1.34 g, 26% w/v) was added into reaction mixture at 35°C under vigorous agitation. Solid compound was precipitated out. Added to the slurry tetrahydrofuran (70 ml) and stirred for 10 minutes. Solid sodium chloride (2 g) was added to the reaction mass and further stirred for 25 minutes after which the layers were separated. The organic layer was dried over powdered molecular sieves (10 g) for sufficient period followed by filtration to remove the molecular sieves. The clear filtrate was concentrated under vacuum to remove remaining water azeotropically with tetrahydrofuran. The crude product obtained after removal of tetrahydrofuran completely was dissolved into fresh tetrahydrofuran (50 ml) and filtered to remove any undissolved particles. The organic layer was concentrated under vacuum at 45°C to remove the solvent completely to get title compound dried under vacuum at 45°C.

Yield: 3.5 g (70%) (XRD as per Figure 1 showed it to be amorphous material)

Example 10: Conversion of Crystalline Rosuvastatin Magnesium to Amorphous Rosuvastatin Magnesium

Crystalline rosuvastatin magnesium (10.0 g) was added into mixture of ethyl acetate (100 ml) and water (100 ml) at room temperature. The pH of the resulting solution was adjusted 4.0 to 4.2 by adding dilute hydrochloric acid at 25°C. The layers were separated and organic layer was washed with water. The solvent was concentrated under vacuum to get oily residue.

The oily residue obtained above was dissolved in methanol (35 ml) and water (50 ml) at room temperature. The pH of the solution was adjusted with sodium hydroxide (8% solution in water) to about 8.5 to 9.0 and the resulting reaction mass was stirred for further 1 hour at room temperature. Methanol was removed under vacuum. The oily residue was reconstituted in water (50 ml) and to the aqueous solution added a solution of magnesium diacetate tetrahydrate (2.8 g) in water (20 ml) at 20-22°C with vigorous stirring. Solid compound was precipitated out. Added to the slurry tetrahydrofuran (50 ml) and stirred for 10 minutes. Solid sodium chloride (2 g) was added to the reaction mass and further stirred for 25 minutes after which the layers were separated. The organic layer was dried over powdered molecular sieves (10 g) for sufficient period followed by filtration to remove the molecular sieves. The clear filtrate was concentrated under vacuum to remove remaining water azeotropically with tetrahydrofuran. The crude product obtained after removal of tetrahydrofuran completely was dissolved into fresh tetrahydrofuran (50 ml) and filtered to remove any undissolved particles. The organic layer was concentrated under vacuum at 45°C to remove the solvent completely to get title compound dried under vacuum at 45°C.

Yield: 7.8 g (78%) (XRD as per Figure 1 showed it to be amorphous material)

Example 11: Preparation of Amorphous Rosuvastatin Magnesium from Rosuvastatin Methyl Ammonium Salt

Rosuvastatin methyl ammonium salt of Formula II (10.0 g) was added into water (50 ml) and to it charged aqueous sodium hydroxide solution (9 ml, 8% w/v) at 25-30°C. The resultant mass was stirred for 20 minutes. The mass was filtered through celite bed and the bed was washed with water (20 ml). From the resultant clear solution water (40 ml) was recovered under vacuum at 60°C followed by addition of further water (40 ml). The mass was further concentrated to recover water (40 ml). After removal of water was added fresh water (40 ml) to the reaction mass. Aqueous solution of Magnesium diacetate tetrahydrate (2.6 g, 26% w/v) was added into reaction mixture at 35°C under vigorous agitation. Solid compound was precipitated out. Added to the slurry tetrahydrofuran (50 ml) and stirred for 10 minutes. Solid sodium chloride (2 g) was added to the reaction mass and further stirred for 25 minutes after which the layers were separated. The organic layer was dried over powdered molecular sieves (10 g) for sufficient period followed by filtration to remove the molecular sieves. The clear filtrate was concentrated under vacuum to remove remaining water azeotropically with tetrahydrofuran. The crude product obtained after removal of tetrahydrofuran completely was dissolved into fresh tetrahydrofuran (50 ml) and filtered to remove any undissolved particles. The organic layer was concentrated under vacuum at 45°C to remove the solvent completely to get title compound dried under vacuum at 45°C.

Yield: 6.5 g (68%) (XRD as per Figure 1 showed it to be amorphous material)

Example 12: Preparation of Amorphous Rosuvastatin Magnesium from Crystalline Rosuvastatin Magnesium

Step A) Preparation of Mixture of Amorphous and Crystalline Rosuvastatin Magnesium

Crystalline rosuvastatin magnesium (6.0 gm) was slurried in cyclohexane (10 ml) and the slurry was placed in a glass mortar. The slurry was triturated with pestle for about 25 to 30 hours. The slurry was then filtered and the solid was dried under vacuum at 40-45°C to get the tile compound.

Yield: 5.43 gm (90%) (XRD as per Figure 3 showed it to be a mixture of amorphous and crystalline material)

Step B) Conversion of Mixture of Amorphous and Crystalline Rosuvastatin Magnesium to Amorphous Rosuvastatin Magnesium

The product obtained in step A) (2.0 g) was dissolved in tetrahydrofuran (5 ml) at 25-30°C. The solution was filtered through celite bed to get a clear solution of rosuvastatin magnesium in tetrahydrofuran and the celite bed was washed with tetrahydrofuran (2 ml). The clear solution was then concentrated and solvent was recovered under vacuum at 45°C to get title product.

Yield: 1.9 g (95%) (XRD as per Figure 1 showed it to be amorphous material)

Example 13: Preparation of Amorphous Rosuvastatin Calcium from Amorphous Rosuvastatin Magnesium

Amorphous rosuvastatin magnesium (10.0 g) was added into mixture of ethyl acetate (100 ml) and water (100 ml) at room temperature. The pH of the resulting solution was adjusted 4.0 to 4.2 by adding dilute hydrochloric acid at 25°C. The layers were separated and organic layer was washed with water. The solvent was concentrated under vacuum to get oily residue.

The oily residue obtained above was dissolved in methanol (35 ml) and water (50 ml) at room temperature. The pH of the solution was adjusted with sodium hydroxide (8% w/v solution in water) to about 8.5 to 9.0 and the resulting reaction mass was stirred for further 1 hour at room temperature. Methanol was removed under vacuum. The oily residue was reconstituted in water (50 ml) and to the aqueous solution added a solution of calcium acetate (2.1 gm) in water (10 ml) at 20-22oC with vigorous stirring. After complete addition, mixture was stirred for further 2 hours at 20-22oC and filtered, washed the cake with water (20 ml) thrice and then dried at 45oC under vacuum to get amorphous rosuvastatin calcium.

Yield: 7.50 gm (75%) (XRD as per Figure 4 showed it to be an amorphous material)

HPLC Purity: 99.52% Diastereomeric impurity: 0.27%

Example 14: Preparation of Crystalline Rosuvastatin Calcium from Amorphous Rosuvastatin Calcium

The product obtained in Example 13 (5.0 gm) was added to a mixture of water (50 ml) and acetonitrile (50 ml) at 15oC. The mixture was warmed to 40oC to obtain complete solution. The mixture was then cooled slowly to 25-30oC and stirred for 16 hours. The crystalline product was separated by filtration at ambient temperature and dried at 50oC under vacuum to give rosuvastatin calcium as white crystals.

Yield: 3.4 gm (68%) (XRD as per Figure 5 showed it to be crystalline material)

We Claim:

1. Amorphous rosuvastatin magnesium.

2. Amorphous rosuvastatin magnesium having purity greater than 99% with diastereomeric impurity less than 0.5%.

3. Amorphous rosuvastatin magnesium according to claim 2 having purity greater than 99.5% with diastereomeric impurity less than 0.25%.

4. Amorphous rosuvastatin magnesium according to claim 3 having purity greater than 99.8% with diastereomeric impurity less than 0.15%.

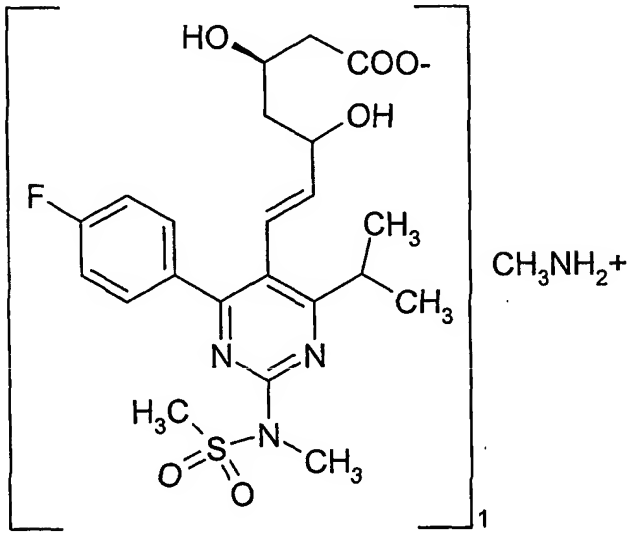
5. Amorphous rosuvastatin magnesium substantially free of crystalline rosuvastatin magnesium.

6. A process for the preparation of crystalline rosuvastatin magnesium comprising:

   a) treating rosuvastatin methyl ammonium salt or rosuvastatin lactone with a base and magnesium salt; and

   b) isolating crystalline rosuvastatin magnesium from the reaction mass.

7. A process for preparation of crystalline rosuvastatin magnesium from rosuvastatin methyl ammonium salt of Formula II,

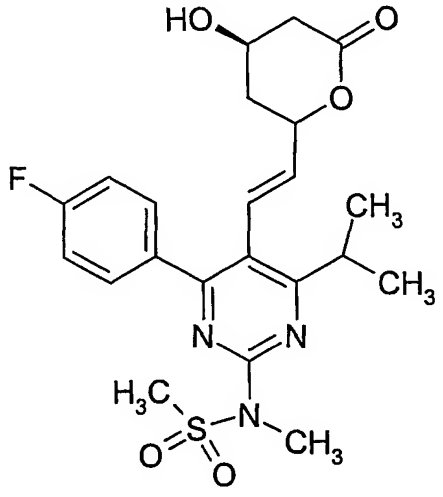


FORMULA II

Comprising;

a) lactonizing the rosuvastatin methyl ammonium salt of Formula II;

b) optionally isolating the rosuvastatin lactone of Formula III;



FORMULA III

c) converting the rosuvastatin lactone to the rosuvastatin magnesium by treatment with a base and a magnesium salt; and

d) recovering the crystalline rosuvastatin magnesium from the reaction mass.

8. A process for preparing amorphous rosuvastatin magnesium comprising:

a) dissolving crystalline rosuvastatin magnesium in an organic solvent;

b) removing the solvent from the solution; and

c) recovering amorphous rosuvastatin magnesium.

9. A process for preparing amorphous rosuvastatin magnesium comprising:

a) dissolving crystalline rosuvastatin magnesium in a first organic solvent;

b) adding a second organic solvent to the solution of rosuvastatin magnesium or adding the solution of rosuvastatin magnesium to the second organic solvent (in optional order of succession) wherein rosuvastatin magnesium is insoluble or very slightly soluble or sparingly soluble in the second solvent, such that amorphous rosuvastatin magnesium precipitates; and

c) isolating amorphous rosuvastatin magnesium.

10. A process for preparing amorphous rosuvastatin magnesium comprising:

a) dissolving crystalline rosuvastatin magnesium in an organic solvent;

b) adding water to the solution of rosuvastatin magnesium, or adding the solution of rosuvastatin magnesium to water (in optional order of succession), such that rosuvastatin magnesium precipitates; and

c) isolating amorphous rosuvastatin magnesium.

11. A process for preparing amorphous rosuvastatin magnesium comprising:

a) subjecting crystalline rosuvastatin magnesium to milling until the crystalline form is converted to the amorphous form; and

b) optionally drying the amorphous form.

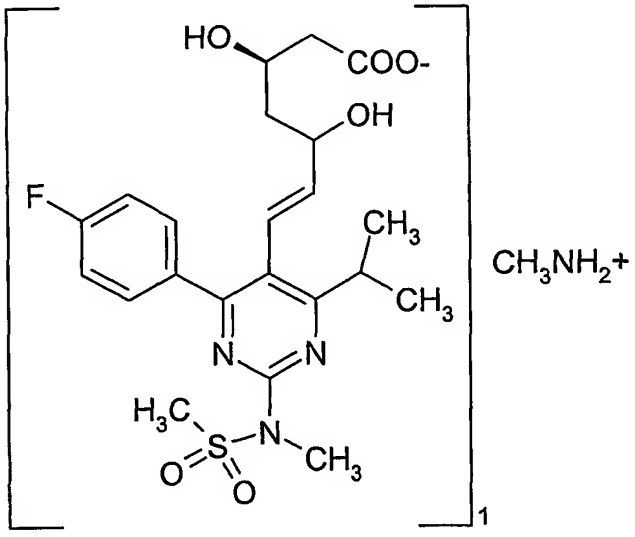
12. A process for preparing amorphous rosuvastatin magnesium comprising:

a) dissolving crystalline rosuvastatin magnesium in an organic solvent optionally containing water; and

b) freeze drying or lyophilizing the solution to get amorphous rosuvastatin magnesium.

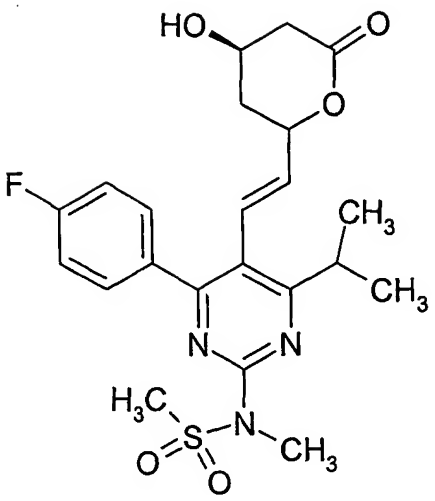
13. A process for preparing amorphous rosuvastatin magnesium comprising:

a) lactonizing rosuvastatin methyl ammonium salt of Formula II; and



FORMULA II

b) optionally isolating the rosuvastatin lactone of Formula III;



FORMULA III

c) converting the lactone form of rosuvastatin to the rosuvastatin magnesium by treatment with a base and a magnesium salt;

d) removing the water from the reaction mass by azeotropic distillation using an organic solvent; and

e) recovering the amorphous form of rosuvastatin magnesium by removing the organic solvent from the resultant solution.

14. A process for preparing amorphous rosuvastatin magnesium comprising:

a) treating crystalline rosuvastatin magnesium with an acid to obtain rosuvastatin;

b) optionally isolating rosuvastatin;

c) converting rosuvastatin to rosuvastatin magnesium by treatment with a base and magnesium salt;

d) removing the water from the reaction mass by azeotropic distillation using an organic solvent; and

e) recovering amorphous rosuvastatin magnesium by removing the organic solvent from the resultant solution.

15. A process for preparation of amorphous rosuvastatin magnesium comprising:

a) treating rosuvastatin methyl ammonium salt with a base and a magnesium salt;

b) removing water from the reaction mass by azeotropic distillation using an organic solvent; and

c) recovering amorphous rosuvastatin magnesium by removing the organic solvent from the resultant solution.

16. A process for preparing rosuvastatin calcium comprising:

a) treating amorphous rosuvastatin magnesium with a base and a calcium salt; and

b) isolating rosuvastatin calcium from the reaction mass.

17. Amorphous rosuvastatin magnesium having an X-ray diffraction pattern as depicted in Figure 1.

18. Pharmaceutical composition to be used as HMG-CoA reductase inhibitor in treatment of hyperlipidemia comprising amorphous rosuvastatin magnesium.

19. A method for inhibiting HMG-CoA enzyme in treatment of hyperlipidemia, comprising administering to a mammal in need thereof a therapeutically effective amount of amorphous rosuvastatin magnesium.

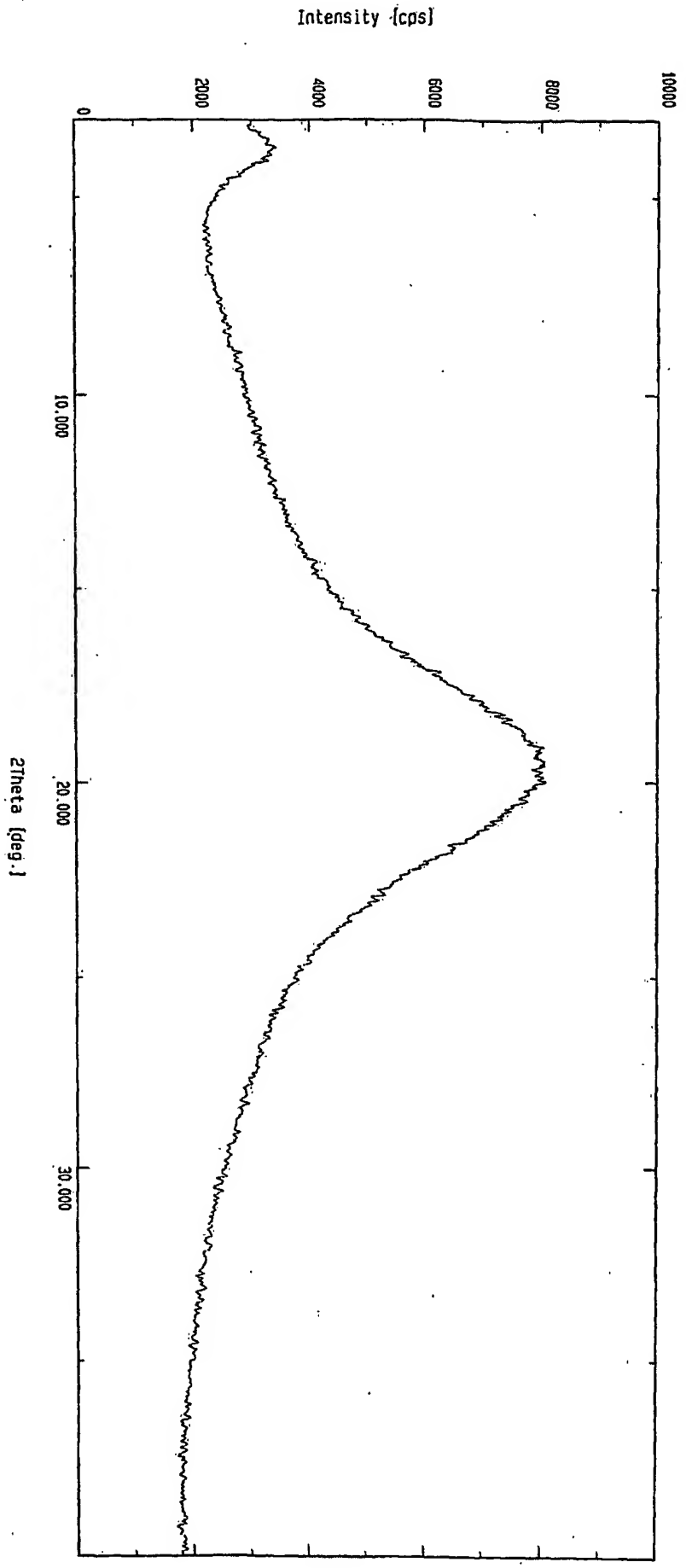

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Figure 1

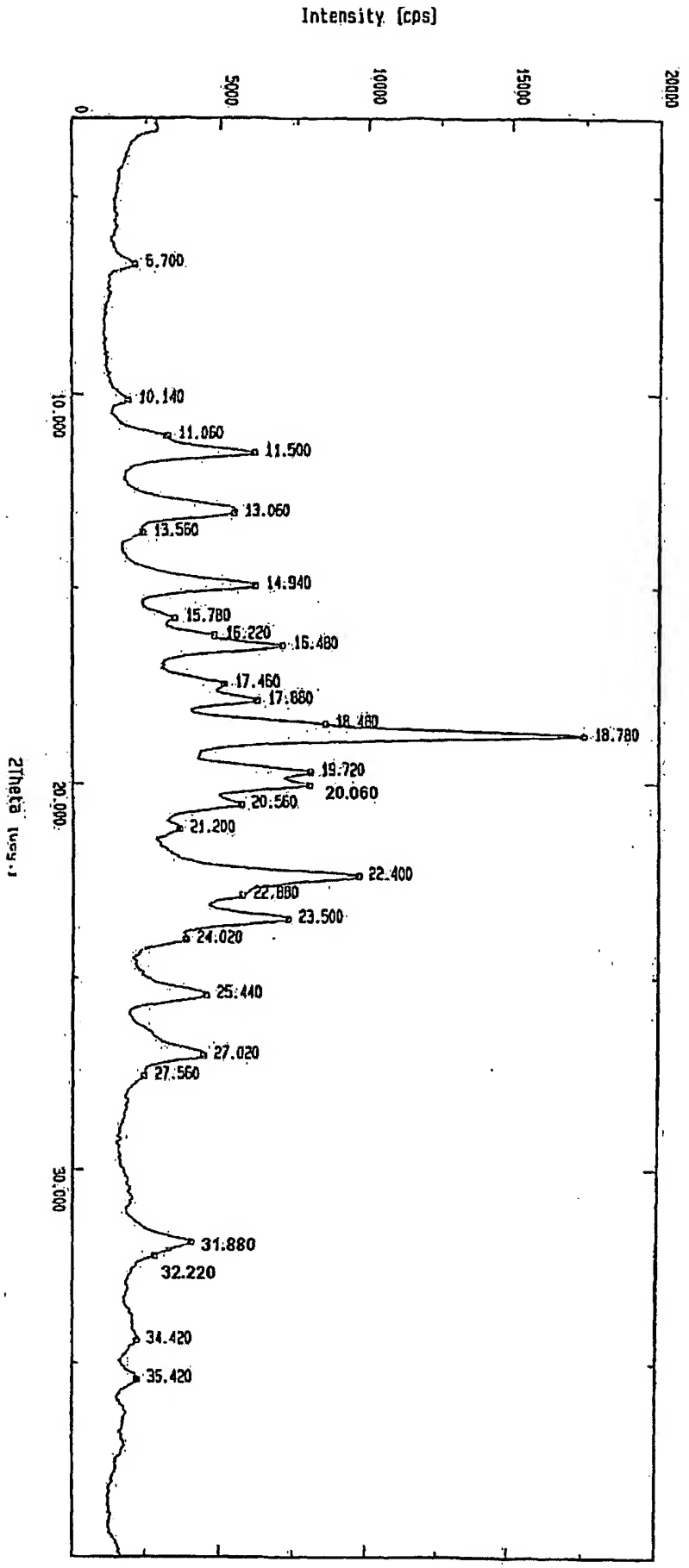
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Figure 2

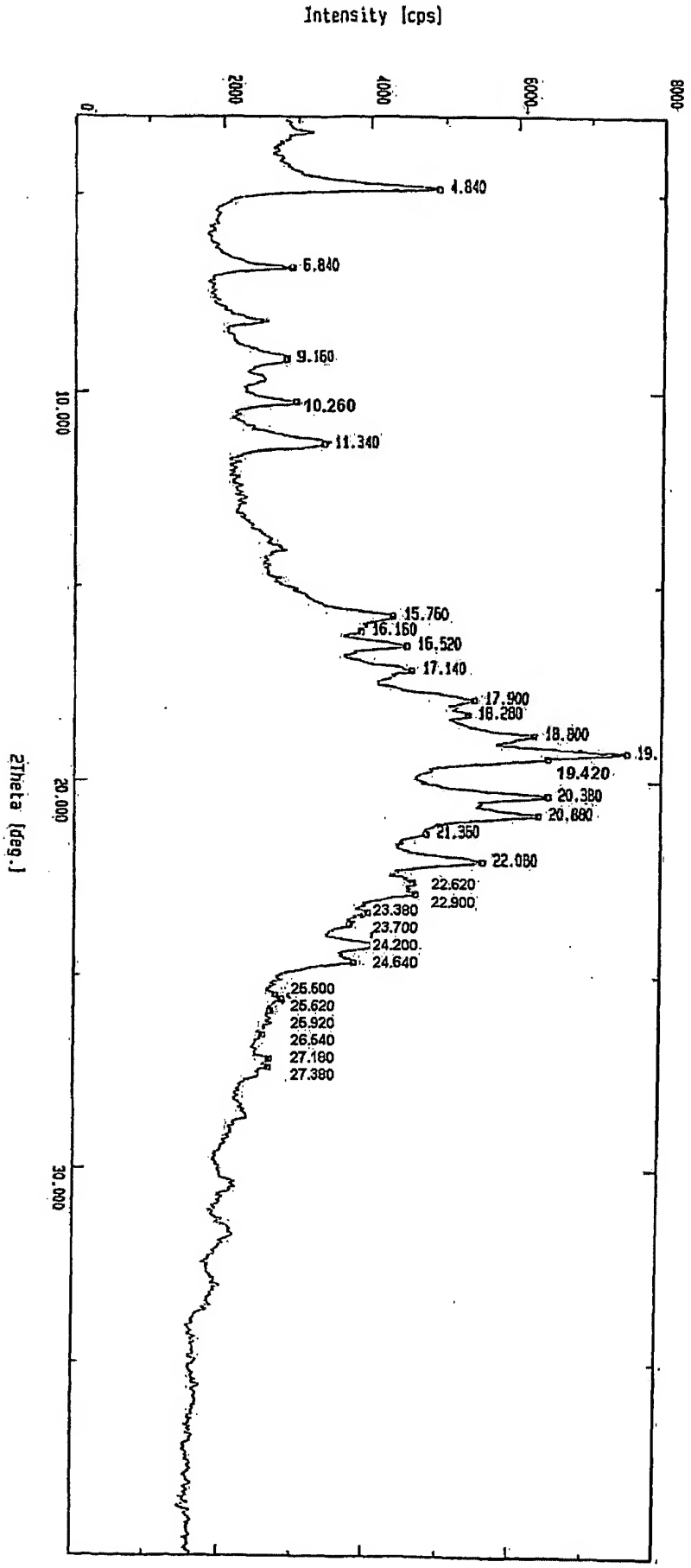
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Figure 3

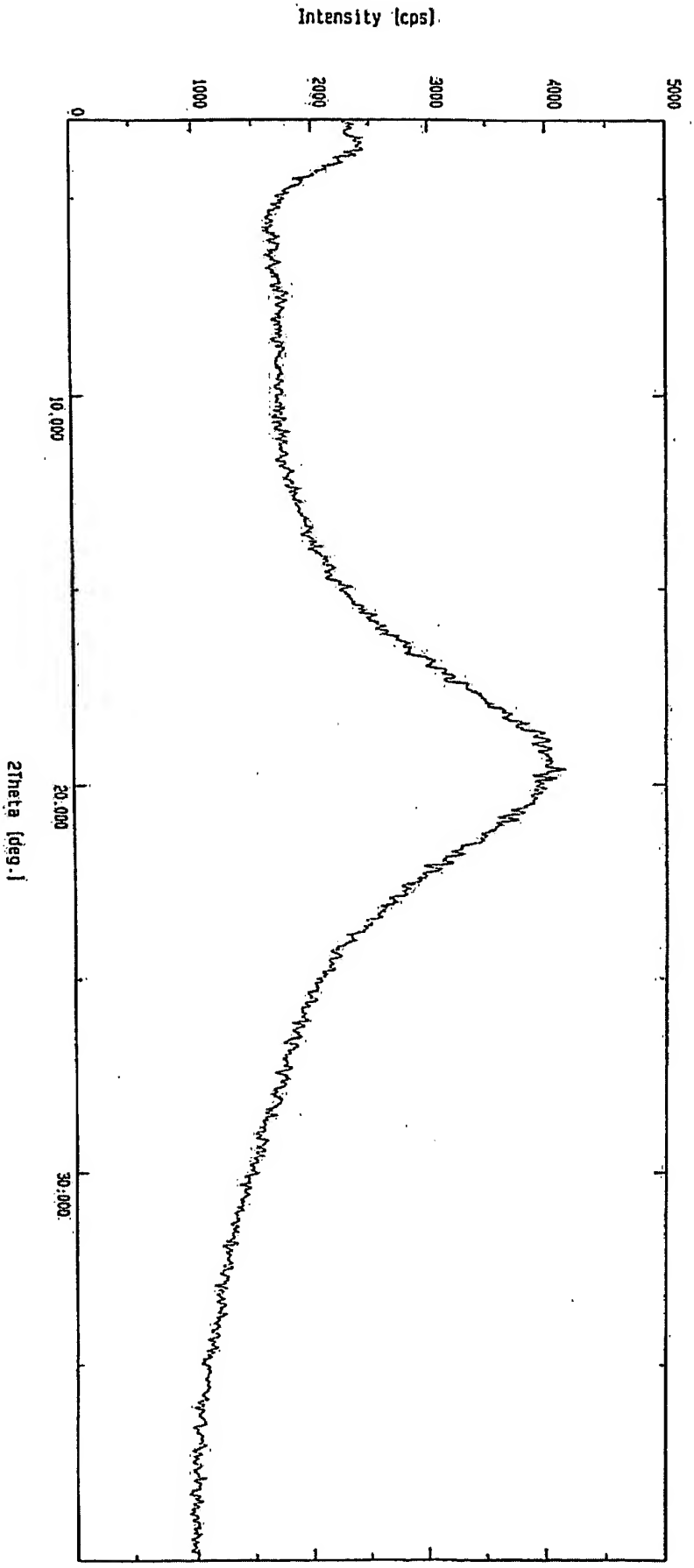
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Figure 4

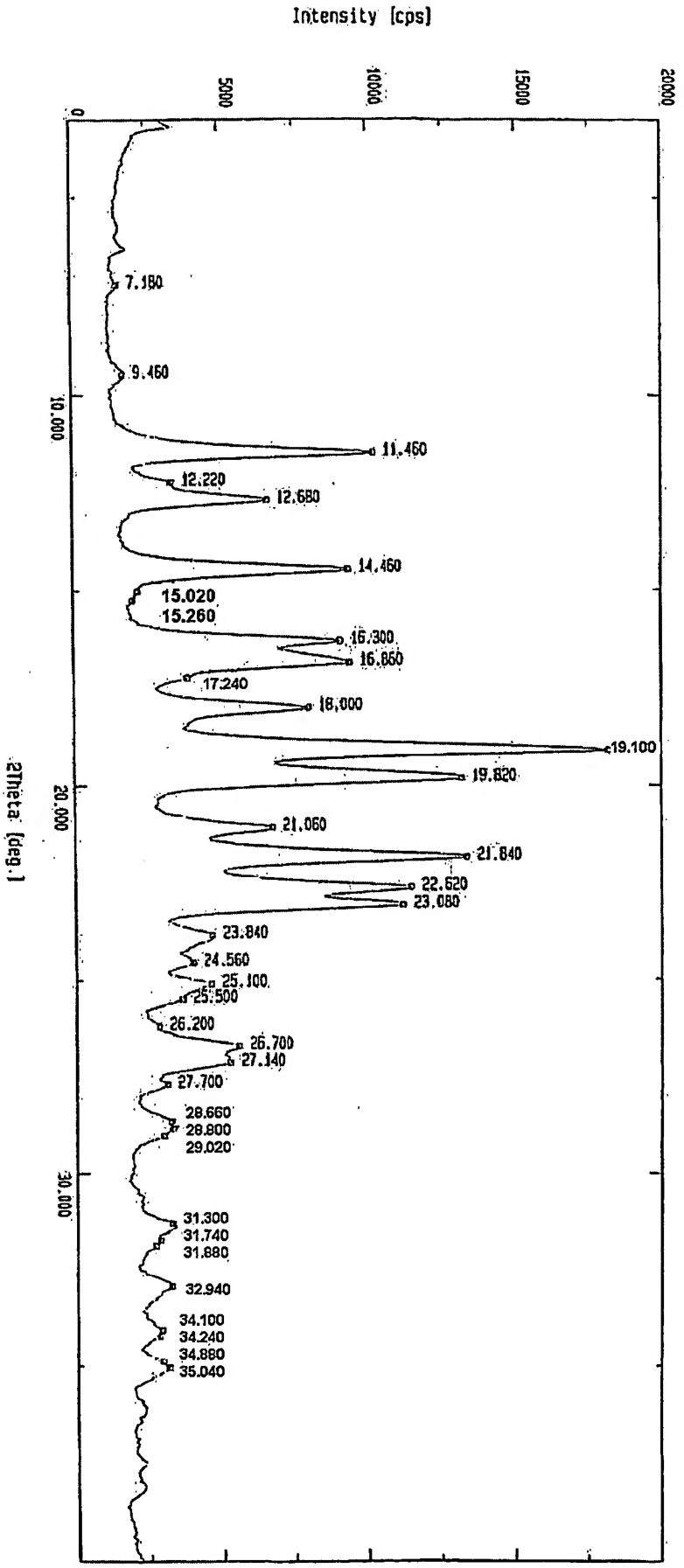
Intensity [cps]
0
5000
10000
15000
20000
2Theta [deg.]
10.000
20.000
30.000
7.180
9.460
11.460
12.220
12.680
14.460
15.020
15.260
16.300
16.860
17.240
18.000
19.100
19.820
21.060
21.840
22.620
23.080
23.840
24.560
25.100
25.500
26.200
26.700
27.140
27.700
28.660
28.800
29.020
31.300
31.740
31.880
32.940
34.100
34.240
34.880
35.040

Figure 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000132

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/60804 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; SHIONOGI & CO., LTD; TAYLOR, N) 23 August 2001 (2001-08-23) cited in the application claim 15; example 10	1-19
X	claims 1,11,15; example 9	6,7
Y	US 6 589 959 B1 (TAYLOR NIGEL P) 8 July 2003 (2003-07-08) cited in the application column 2, lines 11-40	1-19
X	EP 0 521 471 A (SHIONOGI SEIYAKU KABUSHIKI KAISHA) 7 January 1993 (1993-01-07) cited in the application page 2, lines 12-45; claim 1; examples 1,7 page 2, line 53 - page 4, line 15	1-5, 17-19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2005	18.07.05

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schuemacher, A

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/016317 A1 (TEVA PHARMACEUTICAL INDUSTRIES LTD., ISRAEL; TEVA PHARMACEUTICALS USA,) 27 February 2003 (2003-02-27) page 2, lines 15-32; claim 24; examples 7,8	16
P,A	WO 2004/014872 A1 (ASTRAZENECA UK LIMITED, UK) 19 February 2004 (2004-02-19) page 2, lines 18-30; claims 1,15	16
P,X	WO 2004/108691 A1 (ASTRAZENECA UK LIMITED, UK) 16 December 2004 (2004-12-16) page 15, lines 8-15; claim 1	1-19
E	WO 2005/021511 A1 (HETERO DRUGS LIMITED, INDIA) 10 March 2005 (2005-03-10) claims 1,6	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/000132

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5,8-15,17

   amorphous rosuvastatin magnesium salt and the process for its preparation

   ---

2. claims: 6,7

   process for the preparation of crystalline rosuvastatin magnesium salt

   ---

3. claim: 16

   process for the preparation of rosuvastatin calcium salt

   ---

4. claim: 18 and 19

   pharmaceutical composition comprising rosuvastatin magnesium salt and its use as HMG-CoA reductase inhibitor in the treatment of hyperlipidemia

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2005/000132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0160804 A	23-08-2001	AU 775569 B2	05-08-2004
		AU 3208401 A	27-08-2001
		BG 106969 A	30-04-2003
		BR 0108378 A	11-03-2003
		CA 2397450 A1	23-08-2001
		CN 1418198 A	14-05-2003
		CZ 20022754 A3	13-11-2002
		EE 200200445 A	15-12-2003
		EP 1263739 A1	11-12-2002
		WO 0160804 A1	23-08-2001
		HU 0204051 A2	28-05-2003
		JP 2003523334 T	05-08-2003
		NO 20023853 A	14-08-2002
		NZ 520032 A	26-03-2004
		PL 356472 A1	28-06-2004
		SK 11742002 A3	04-02-2003
		US 2003045718 A1	06-03-2003
		ZA 200205331 A	03-10-2003
US 6589959 B1	08-07-2003	AT 282027 T	15-11-2004
		AU 762909 B2	10-07-2003
		AU 1882600 A	01-08-2000
		BR 9916786 A	16-10-2001
		CA 2356212 A1	20-07-2000
		CN 1333756 A	30-01-2002
		CZ 20012460 A3	17-10-2001
		DE 69921855 D1	16-12-2004
		EE 200100359 A	16-12-2002
		EP 1144389 A1	17-10-2001
		ES 2232194 T3	16-05-2005
		WO 0042024 A1	20-07-2000
		HK 1040989 A1	06-05-2005
		HU 0104828 A2	29-07-2002
		ID 29432 A	30-08-2001
		JP 2002539078 T	19-11-2002
		NO 20013368 A	05-09-2001
		NZ 512560 A	29-08-2003
		PL 348775 A1	17-06-2002
		RU 2236404 C2	20-09-2004
		SK 9632001 A3	03-12-2001
		TR 200101894 T2	21-12-2001
		US 2004009997 A1	15-01-2004
		ZA 200105187 A	23-09-2002
EP 0521471 A	07-01-1993	AT 197149 T	15-11-2000
		CA 2072945 A1	02-01-1993
		CY 2226 A	18-04-2003
		DE 69231530 D1	30-11-2000
		DE 69231530 T2	13-06-2001
		DK 521471 T3	05-02-2001
		EP 0521471 A1	07-01-1993
		ES 2153824 T3	16-03-2001
		GR 3035189 T3	30-04-2001
		HK 1011986 A1	13-07-2001
		HU 220624 B1	28-03-2002
		HU 61531 A2	28-01-1993
		JP 2648897 B2	03-09-1997
		JP 5178841 A	20-07-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2005/000132

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0521471 A		KR	9605951 B1	06-05-1996
		LU	91042 A9	24-11-2003
		NL	300125 I1	01-07-2003
		PT	521471 T	30-04-2001
		US	RE37314 E1	07-08-2001
		US	5260440 A	09-11-1993
WO 03016317 A1	27-02-2003	US	2002099224 A1	25-07-2002
		CA	2450820 A1	27-02-2003
		CN	1543468 A	03-11-2004
		CZ	20040337 A3	12-01-2005
		EP	1425287 A1	09-06-2004
		HR	20040255 A2	31-08-2004
		JP	2005500382 T	06-01-2005
		NZ	529913 A	24-03-2005
		SK	1402004 A3	03-01-2005
		TR	200302281 T2	21-09-2004
		US	2003114685 A1	19-06-2003
		US	2004176615 A1	09-09-2004
		ZA	200309373 A	02-12-2004
WO 2004014872 A1	19-02-2004	AU	2003251369 A1	25-02-2004
		CA	2495296 A1	19-02-2004
		EP	1539711 A1	15-06-2005
WO 2004108691 A1	16-12-2004	NONE		
WO 2005021511 A1	10-03-2005	AU	2003269478 A1	16-03-2005